201-14282A

TEST PLAN AND CATEGORY JUSTIFICATION FOR CHLOROBENZENES CATEGORY

January 29, 2003

OVERVIEW

The SOCMA Chlorobenzene Producers Association (CPA) submits the following test plan and category justification for review under the Environmental Protection Agency's High Production Volume Chemical Challenge Program. The category consists of four chlorobenzenes – monochlorobenzene, 1,2-dichlorobenzene, 1,3-dichlorobenzene and 1,2,3-trichlorobenzene. This test plan will also utilize information for two closely related surrogates – 1,4-dichlorobenzene and 1,2,4-trichlorobenzene.

The sponsors conclude that the category approach is valid for the chosen members and surrogates, and that existing studies for category members and the closely related surrogates meet the screening data needs for this category.

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1. Identification of Category Sponsors

The Chlorobenzenes Category is being sponsored by the Chlorobenzenes Producers Association (CPA) under the umbrella of the Synthetic Organic Chemical Manufacturers Association (SOCMA). The following companies are members of CPA:

PPG Industries, Inc.
Solutia Inc.
Metachem Products, LLC
Bayer Corporation

2. Introduction and Identification of Category Members and Data-Rich Surrogates

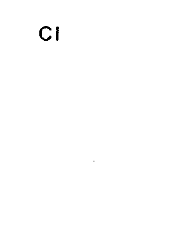
The EPA's "Chemical Categories" guidance sets forth a definition of what constitutes a "chemical category, for the purposes of the Challenge Program." Specifically, that definition states that a chemical category under the HPV Challenge Program "is a group of chemicals whose physicochemical and toxicological properties *are likely to* be similar *or* follow a regular pattern as a result of structural similarity." The Chlorobenzenes Category has been selected with this guidance in mind.

The close similarity in molecular structure of category members and surrogates is shown below. The close similarity of chemical/physical properties, environmental fate parameters, and toxicological properties for the standard screening endpoints is documented in Tables 1-10. Section 4 discusses existing studies available for each endpoint, notes which data gaps exist for particular category members, and discusses the surrogate studies that were selected to characterize each endpoint where needed. Additional details for each study selected are given in the robust summary/dossier sets for each category member. It is the Chlorobenzenes Producers Association's conclusion that adequate studies exist and are summarized to satisfy the screening data needs for all category members.

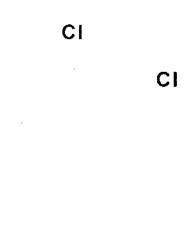
The general chemical formula of the category members and surrogates is depicted as:

$C_6H_{6-n}Cl_n$, where n = 1, 2 or 3

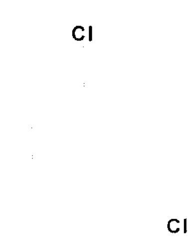
<u>The **category** consists of the following members:</u>



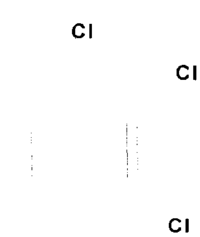
Monochlorobenzene
CAS No. 108-90-7



1,2-Dichlorobenzene
CAS No. 95-50-1

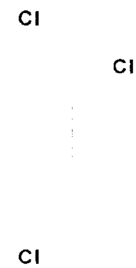


1,3-Dichlorobenzene
CAS No. 541-73-1



1,2,3-Trichlorbenzene
CAS No. 87-61-6

The **surrogates*** are:



1,4-Dichlorobenzene
CAS No. 106-46-7

1,2,4-Trichlorobenzene
CAS No. 120-82-1

*The surrogates have been previously reviewed in the OECD/SIDS program.

3. Category Analysis

All four category members and the two surrogates (as shown above) have closely related chemical structures which are characterized as a benzene ring in which one, two or three aromatic hydrogen atoms are replaced by chlorine atoms. In addition, the two dichlorobenzenes that are category members (1,2- and 1,3-dichlorobenzene) differ from the surrogate 1,4-dichlorobenzene only in the relative placement of the chloro groups on the benzene ring. Finally, category member 1,2,3-trichlorobenzene and surrogate 1,2,4-trichlorobenzene are also isomers, where the only difference is the relative placement of the chloro groups on the benzene ring.

4. Test Plan

Criteria for Determining Adequacy of Data

All available studies were reviewed and assessed for adequacy according to the standards of Klimisch et al. (1). Studies receiving a Klimisch rating of 1 or 2 are considered to be adequate. Studies from other category members and surrogates were used to support studies assigned a reliability rating of 4 (not assignable).

Test Plan Matrix

The Chlorobenzenes Category test plan matrix (as shown in Table 1) was constructed after a careful evaluation of all existing data (see Section 4 below). This matrix is arranged by category members (columns) and screening data endpoints (rows), and indicates how data are provided for each end point in the sets of robust summaries.

Table 1. Test Plan Matrix for Chlorobenzenes Category

	108-90-7 (monochloro-benzene)	95-50-1 (1,2-dichloro-benzene)	541-73-1 (1,3-dichloro-benzene)	87-61-6 (1,2,3-tri-chlorobenzene)
ENDPOINT				
PHYSICAL CHEMISTRY				
Melting point	Y	Y	Y	Y
Boiling point	Y	Y	Y	Y
Density	Y	Y	Y	Y
Vapor Pressure	Y	Y	Y	Y
Water Solubility	Y	Y	Y	Y
Kow	Y	Y	Y	E
ENVIRONMENTAL FATE				
Photodegradation	E	E	E	E
Stability in Water	E	Y	E	E
Biodegradation	Y	Y	Y	C
Transport between Environmental Compartments (Fugacity)	E	E	E	E
ECOTOXICITY				
Acute Toxicity to Fish	Y	Y	Y	Y
Acute Toxicity to Aquatic Invertebrates	Y	Y	Y	Y
Toxicity to Aquatic Plants	Y	Y	Y	Y
TOXICOLOGICAL DATA				
Acute Toxicity	Y	Y	Y	C
Repeated Dose Toxicity	Y	Y	Y	Y
Genetic Toxicity-Mutation	Y	Y	Y	Y
Genetic Toxicity-Chromosomal Aberrations	Y	Y	C	Y
Carcinogenicity	Y	Y	NR	NR
Toxicity to Reproduction	Y	Y	C	C
Developmental Toxicity	Y	Y	C	Y

Y = adequate experimental data; E = Endpoint fulfilled via estimation; C = endpoint fulfilled by other category members and/or surrogates; NR = not required

4.1 Chemical/Physical Properties

A large body of published information exists for chemical physical properties of chlorobenzenes. Category members and surrogates are generally similar in chemical/physical properties (Table 2). Most are liquids, although the 1,4-isomer has a higher melting point and is a solid (1,4-substituted aromatics tend to have higher melting points for other substituents as well). Boiling points, range from 132-221°C and vapor pressures @20°C for all category members tend to be low. Category members and surrogates have relatively low water solubilities and positive log Kows (which range from 2.84-3.93).

Table 2. Chemical/Physical Properties of Category Members and Surrogates

Chemical[a]	Melting Point (°C)	Boiling Point[b] (°C)	Vapor Press. (hPa)	Density (g/cm^3)	Water Sol. (mg/l)	Log Kow
Monochlorobenzene CAS No. 108-90-7	-45.2 (2)	132.1 (2)	11.7^{d} (3)	1.06^{d} (3)	210^{d} (3)	2.84^{g} 2.84^{d} (4-6)
1,2-Dichlorobenzene CAS No. 95-50-1	-17 (2)	180.5 (2)	1.3^{d} (2)	1.298^{d} (7)	145^{c} (2)	3.28^{g} 3.43 (8,9)
1,3-Dichlorobenzene CAS No. 541-73-1	-25.5 (10)	173 (10)	1.8^{d} (10)	1.29^{d} (10)	100^{d} (10)	3.28^{g} 3.38 (10)
1,4-Dichlorobenzene CAS No. 106-46-7	53.5 (3)	174 (3)	0.8^{d} (3)	1.231^{f} (3)	60^{d} (3)	3.28^{g} 3.39 (11)
1,2,3-Trichlorobenzene CAS No. 87-61-6	52.6 (12)	221 (12)	1.33^{e} (12)	1.69^{c} (12)	Insol (12) 17.38^{g}	3.93^{g}
1,2,4-Trichlorobenzene CAS No. 120-82-1	17 (10)	213 (10)	0.36^{f} (10)	1.45^{d} (10)	49 (10)	3.93^{g}

[a]Category members are in bold face and surrogates are in regular type. References for published data are numbered in parentheses. The robust summary for the log Kow for 1,4-dichlorobenzene is located in the file for 1,3-dichlorobenzene (CAS No. 541-73-1).

[b] at 1013 hPa, [c] at 25 °C, [d] at 20 °C, [e] at 40 °C, [f] at 70 degrees C

[g] Estimated using EPIWIN [The EPI (Estimation Programs Interface) Suite™ developed by the Environmental Protection Agency Office of Pollution Prevention Toxics and Syracuse Research Corporation (SRC)(2000)].

4.2 Environmental Fate/Pathways

A large body of published information is available with respect to environmental fate of chlorobenzenes (4,8,13). Available measured values for Henry's Law and photodegradation rate constants are provided in Table 3. Where measured values were not available, values were estimated (calculated) using EPIWIN modeling and similar approaches. Estimated values are in close agreement with experimental values. Summaries of both Level I and Level III fugacity modeling are provided. As shown in Table 3 below, environmental fate parameters are consistent for category members and their surrogates.

Table 3. Comparison of environmental fate parameters for category members and surrogates

Chemical[a]	Henry's Law Constant (atm-m^3/ mole)	Photodeg. OH radical rate constant[b] (cm^3/molecule-sec)	Predicted Environmental Distribution[b]					
			Level III				Level I	
			Air (%)	Water (%)	Soil (%)	Sed. (%)	Air (%)	Soil (%)
Monochlorobenzene CAS No. 108-90-7	0.00311[b] 0.00393 (4, 14)	0.77E-12	25.5	31.1	43.1	0.264	97.9	0.7
1,2-Dichlorobenzene CAS No. 95-50-1	0.00192[b] 0.00170 (8, 15)	0.400E-12	12.4	19	67.9	0.72	94.0	4.0
1,3-Dichlorobenzene CAS No. 541-73-1	0.00263[b]	0.69E-12 (10)	13.1	20.21	66	0.75	96.0	3.0
1,4-Dichlorobenzene CAS No. 106-46-7	0.00241[b]	0.4005E-12	13.1	19.1	67	0.801	91.0	6.0
1,2,3-Trichlorobenzene CAS No. 87-61-6	0.00125[b]	0.2817E-12	6.45	11.9	79.1	2.55	79.7	18.2
1,2,4-Trichlorobenzene CAS No. 120-82-1	0.00142[b]	0.2817E-12	6.27	12	79.4	2.4	81.8	16.3

[a] Category members are in bold face and surrogates are in regular type. References for published data are numbered in parentheses. Refer to robust summaries (IUCLID Section 3) for additional information on category members. Data for the surrogates are in the summary set for 1,2,3-trichlorobenzene.
[b] Estimated using EPIWIN Model calculation for Level III and (16) MacLeod, MacKay (1999) for Level I.

Henry's Law Constants for category members and surrogates fall in the relatively narrow range of 0.00125 to 0.00311 atm-m^3/mol. These values, together with generally low water solubility are consistent with the Fugacity Levels I and III modeling, which predict significant air volatization from surface water. Estimated photodegradation hydroxyl radical rate constants range from 0.28 to 0.77 E-12 cm^3/molecule-sec.

The EPIWIN/HYDROWIN program is not able to estimate stability in water (hydrolysis) for chlorobenzenes. Chlorobenzenes generally do not hydrolyze readily under neutral ambient conditions, but hydrolyze to phenols in dilute aqueous solution of alkali at high temperature and pressure (17). The half-life of 1,2-dichlorobenzene in water from pH 3-11 ranges from 35-45 days (18). Therefore, water hydrolysis is unlikely to be an important degradative pathway in natural environmental systems and no additional hydrolysis testing is planned.

Level I and Level III fugacity modeling (environmental transport) provide useful data in predicting distribution of chlorobenzenes in various environmental media (16). Level I modeling indicates that under equilibrium, steady state conditions, the bulk of chemical released will reside in either air or soil, with over 90% of mono- and di-chlorobenzenes, and 79.7% of 1,2,3-trichlorobenzene residing in the air. Level III modeling allows non-equilibrium conditions to exist between connected media at steady state. The tendency of chemicals to migrate between media can be assessed by modeling emissions to each individual medium and calculating the amount present at steady state. Level III modeling predicts that for mono-, di-, and trichlorobenzenes, emissions tend to remain in the medium of release and are removed by advection or degradation. Emissions of chlorobenzenes to soil are predicted to remain predominately in soil, with only the relatively volatile monochlorobenzene moving significantly to air. Mono-, di- and tri- chlorobenzenes emitted to the air tend to remain in the atmosphere and undergo photodegradation. When emitted to water, these relatively insoluble and volatile chlorobenzenes tend to volatilize to the atmosphere. Photodegradation in the hydrosphere (aqueous environment) is not considered to be an important elimination mechanism for chlorobenzenes (4,8).

4.3 Biodegradation

Biodegradation data are available for all category members and surrogates (except 1,2,3-trichlorobenzene). As shown in Table 4, biodegradation rates for the category members and surrogates vary depending on the type of test used.

Table 4. Comparison of biodegradation rate ranges for category members and surrogates

Category Member[a]	Biodegradation Rate
Monochlorobenzene (3) **CAS No. 108-90-7**	> 90% after 15 days (respirometer test with sludge) 76.7% after 2 months (ground water microcosm) 50-60% after 20 days (OECD 301D: Ready Biodegradability: Closed Bottle Test) 0-15% after 28 days (modified MITI test)
1,2-Dichlorobenzene (7) **CAS No. 95-50-1**	92-96% after 7 days (respirometer, activated sludge) 58% after 20 days (OECD 301D: Ready Biodegradability: Closed Bottle Test) 0% after 28 days (MITI test)
1,3-Dichlorobenzene (10) **CAS No. 541-73-1**	100% after 96 hours (respirometer test with Pseudomonas sp.) 58 % after 7 days (activated sludge) 0% after 28 days (OECD 301C: modified MITI test)
1,4-Dichlorobenzene (3) CAS No. 106-46-7	20% after 15 days (industrial, non-adapted sludge)
1,2,3-Trichlorobenzene **CAS No. 87-61-6**	Data from other category members
1,2,4-Trichlorobenzene (10) CAS No. 120-82-1	56% after 5 days (activated sludge) 0% after 14 days (MITI test)

[a] Category members are in bold face and surrogates are in regular type. References are indicated numerically in parentheses. See robust summaries (IUCLID Section 3.5) for study details.

Results of respirometer tests with sludge show greater than 90% biodegradability of monochlorobenzene and 1,2-dichlorobenzene. OECD 301D closed bottle tests for monochlorobenzene and 1,2-dichlorobenzene indicate 50-60% biodegradability after 20 days. Pseudomonas has been shown to degrade 1,3-dichlorobenzene, and 1,2,4-trichlorobenzene. By contrast, results of MITI tests show poor biodegradation of chlorobenzenes. Studies with results showing biodegradability generally employed aerobic systems with lower test material concentrations and/or acclimated bacteria.

Based on the structural and physical similarities of 1,2,3- trichlorobenzene with the category members, this material is also expected to biodegrade in the environment. No additional biodegradation testing is recommended.

4.4 Aquatic Toxicity

The category members have been tested in wide variety aquatic species. Due to their potential to volatilize, only tests that employed analytical determinations of test material concentrations and/or closed systems in which care was taken to minimize volatization were reviewed and summarized. As shown in Table 5, such studies have been performed for all category members. Therefore, no additional testing is planned. The LC_{50} values for the category members and surrogates in fish and invertebrates (Daphnia and Mysidopsis bahia) and the EC_{50} values for algae fall within the range of 0.35 to 12.5 mg/l. Values estimated using the ECOSAR program are in close agreement with measured values. It should be noted that results from different exposure durations and different species are included in the table.

Table 5. Comparative aquatic toxicity of category members and surrogates

Chemical[a]	Fish LC_{50} (mg/l)[b]	Invertebrate LC_{50} (mg/l)[c]	Algae EC_{50} (mg/l)[d]
Monochlorobenzene **CAS No. 108-90-7**	4.1 to 10.5 (19,20) 13.545[d,g]	4.3[e] (19) 15.381[f,g]	12.5 (21) 10.092[g]
1,2-Dichlorobenzene **CAS No. 95-50-1**	2.3 to 9.47 (19,22) 5.379[d,g]	0.78[e] (19) 6.345[f,g]	2.2 (21) 4.297[g]
1,3-Dichlorobenzene **CAS No. 541-73-1**	8.03[d] (22) 5.497[d,g]	7.2[f] (23) 6.479[f,g]	7.3 (10) 4.386[g]
1,4-Dichlorobenzene CAS No. 106-46-7	1.18 and 4.25 (19)	1.6[e] (19)	1.6 (21)
1,2,3-Trichlorobenzene **CAS No. 87-61-6**	0.71 to 3.1 (19,24) 2.063[g]	0.35[e] to 2.71[f] (19,25) 0.35[d] (M. bahia) (26) 2.526[f,g]	0.9 (21) 1.765[g]
1,2,4-Trichlorobenzene CAS No. 120-82-1	1.95 and 6.3 (19)	1.2[e] and 1.7[f] (19,23) 0.49[d] (M. bahia) (27)	1.4 (21)

[a] Category members are in bold face and surrogates are in regular type. References are indicated numerically in parentheses. Study details for category members are found in the robust summaries (IUCLID Section 4).
LC50 = lethal concentration in 50% of organisms, EC_{50} = concentration required for 50% inhibition of growth
[b] Values presented are for tests ranging in time from 24 to 96 hours unless otherwise indicated (with highest value not necessarily from 24 hour experiment)
[c] Values are for Daphnia unless otherwise indicated
[d] 96 hours, [e] 24 hours, [f] 48 hours, [g] Estimated using ECOSAR program

4.5 Mammalian Toxicity

4.5.1 Acute

Acute toxicity data for the category members and surrogates in rats and mice were reviewed and summarized (if available). The data in Table 6 show that the category members and surrogates exhibit low toxicity by the oral (LD_{50} values from 756 to 3800 mg/kg), inhalation (LC_{50} values from 1236 - 2965 ppm) and dermal route (LD_{50} values of > 2000 mg/kg). Based on the structural and physical similarities between the members of the category and surrogates, existing data are expected to be predictive of acute oral, inhalation and dermal toxicity of 1,2,3-trichlorobenzene, acute inhalation toxicity of 1,3-dichlorobenzene, and acute dermal toxicity of 1,2-dichlorobenzene. Therefore, no new testing is planned.

Table 6. Acute mammalian toxicity for category members and surrogates

Category member[a]	Acute Oral LD_{50} (mg/kg)	Acute Inhalation LC_{50} (ppm)	Acute Dermal LD_{50} (mg/kg)
Monochlorobenzene CAS No. 108-90-7	1540 (rat) (28) < 1000 (mouse) (29,30)	2965 (rat) (31) 1886 (mouse) (32)	> 7940 (rabbit)[b] (28)
1,2-Dichlorobenzene CAS No. 95-50-1	> 800 and < 2000(g. pig) (33) Rat and mouse data from category members and surrogates	1532 (rat) (31) 1236 (mouse) (32)	Data from category members and surrogates
1,3-Dichlorobenzene CAS No. 541-73-1	1100 (rat) (34)	Data from category members and surrogates	>2000 (rabbit)[b] (34)
1,4-Dichlorobenzene CAS No. 106-46-7	ca. 3800 (rat) (35)	> 997 (rat) (36)	> 6000 (rat) (35)
1,2,3-Trichlorobenzene CAS No. 87-61-6	Data from category members and surrogates	Data from category members and surrogates	Data from category members and surrogates
1,2,4-Trichlorobenzene CAS No. 120-82-1	756 (rat) (37) 766 (mouse) (37)	NA	6139 (rat) (37)

a Category members are in bold face and surrogates are in regular type. References are indicated numerically in parentheses. Study details are found in the robust summaries (IUCLID Section 5.1). NA = not available
LD_{50} = lethal dose in 50% of animals; LC_{50} = lethal concentration in 50% of animals
[b] assigned a reliability rating of 4

4.5.2 Repeated Dose

A number of repeated dose toxicity studies have been conducted for the category members and surrogates. Results of well-conducted ninety-day oral toxicity studies are summarized. As noted in Table 7, adequate subchronic oral studies have been performed on all category members.

In addition, well-conducted repeated dose inhalation studies have been performed on monochlorobenzene (38), 1,2-dichlorobenzene (33), and 1,4-dichlorobenzene (see 2-generation reproductive toxicity study summarized in Section 4.5.3 below)(39). In general, the oral NOAELs are less than 100 mg/kg/day (oral). For all category members and surrogates, the liver and kidney have been identified as target organs in rats and mice (in both oral and inhalation studies). These organs are also targets of monochlorobenzene repeated-dose toxicity in dogs.

Table 7. Repeated dose oral toxicity for category members and surrogates

Category Member[a]	Species/ Exposure	Dose[b] (deaths)	Gross Changes	Histopathological Changes	Clin. Chem/Hemat. Changes
Monochloro benzene CAS No. 108-90-7	F344 Rat Gavage 91 days, 5 days/wk (29, 30)	60 (0/20)	↓ spleen wt	none	none
		125 (0/20)[c]	↓ spleen wt, ↑ liver wt	none	none
		250 (0/20)	↓ spleen wt, bw; ↑ liver wt	liver (minimal)	none
		500 (7/20)	↓ spleen wt, bw; ↑ liver, kidney wt.	liver, kidney, bone marrow	↑ GGT, AP, porphyrin
		750 (17/20)	↓ spleen wt, bw; ↑ liver, kidney wt	liver, kidney, bone marrow, thymus, spleen	↑ GGT, AP, porphyrin, diuresis, ↓ leukocytes
	B6C3F1 Mouse Gavage 91 days, 5 days/wk (29, 30)	60 (0/20)	↓ bw (males)	liver (1/20)	none
		125 (0/20)[c]	↓ bw, ↑ liver wt (males)	liver (1/20)	none
		250 (9/19)	↓, bw, ↑ liver wt	liver, kidney, bone marrow, thymus, spleen	↑ porphyrin
			↑ liver wt, ↓ bw		
		500 (17/20)	no data	same as above	↑ diuresis, porphyrin
		750 (20/20)		liver, kidney, thymus, spleen	no data
	Beagle dog Oral capsule 93 days, 5 days/wk (40)	27.25 (0/8)	none	none	none
		54.5 (0/8)[c]	none	none	none
		272.5 (4/8)	↑ liver, kidney, adrenal, heart, thyroid wt	liver, kidney, hematopoetic tissue, GI tract	↑ GPT, AP, bilirubin, leukocytes, hematocrit, cholesterol, ↓ blood sugar
1,2-Dichloro benzene CAS No. 95-50-1	SD Rat Gavage 90 days, 7 days/wk (41)	25 (0/20)[c]	none	none	none
		100 (0/20)	↑ liver, kidney wt	none	↑ ALT
		400 (0/20)	↑ liver, kidney, heart, brain, lung, testes wt, ↓spleen wt, bw	liver	↑ erythrocytes, ALT, BUN, bilirubin
	F344 Rat Gavage 91 days, 7 days/wk (42)	30 (1/20)	none	none	↑ protein, glucose, cholesterol
		60 (0/20)[c]	none	none	↑ platelets, protein
		125 (1/20)	↑ liver wt	liver (1 female)	↑ platelets, protein, cholesterol, glucose
		250 (0/20)	↑ liver wt	liver	same as above
		500 (2/20)	↑ liver, lung, kidney, brain wt; ↓ thymus, heart, spleen, testicle, uterus wt	liver, kidney, thymus	several hematological changes, ↑ bilirubin, globulin, diuresis, porphyrins, glucose cholesterol, protein
	B6C3F1 Mouse Gavage 91 days, 5 days/wk (42)	30 (0/20)	↓ spleen wt	none	↑WBC (males)
		60 (0/20)	↓ spleen wt	none	↑WBC (males)
		125 (0/20)[c]	↓ spleen wt	none	↑WBC (males)
		250 (0/20)	↓ spleen wt	liver	↑WBC (males)
		500 (7/20)	↑ liver wt , ↓ spleen wt	liver, heart, skeletal muscle, thymus, spleen	↑WBC (males) porphyrins

Table 7 (cont'd). Repeated dose oral toxicity for category members and surrogates

Category Member[a]	Species/ Exposure	Dose[b] (deaths)	Gross Changes	Histopathological Changes	Clin. Chem/Hemat. Changes
1,3-Dichloro benzene CAS No. 541-73-1	SD rat Gavage 90 days (daily) (43)	9 (0/20) 37 (0/20)[c] 147 (0/20) 588 (0/20)	none none ↑ liver, kidney wt, ↓ brain wt. ↑ water consump, liver, kidney, brain, testes wt, ↓ brain bw	thyroid, pituitary[d] thyroid, pituitary[e] liver, thyroid, pituitary[e] liver, thyroid, pituitary[f]	↑ AST, cholesterol ↑ cholesterol, calcium ↑ AST, cholesterol, calcium, WBC ↑ AST, cholesterol, calcium, WBC, RBC, ↓ BUN
1,4-Dichloro benzene CAS No. 106-46-7	F344 Rat Gavage 91 days, 5 days/wk (44)	37.5 (0/20) 75(0/20) 150 (0/20)[c] 300 (7/20) 600 (11/20)	none none none none none	none none none none kidney	not performed
	B6C3F1 Mouse Gavage 91 days, 5 days/wk (44)	84.4 (2/20) 168.8 (2/20)[c] 337.5 (1/20) 675 (3/20) 900 (0/20)	none none none none none	none none none liver liver	not performed
1,2,3-Trichloro benzene CAS No. 87-61-6	SD rat, oral feed, 13 weeks, daily[g] (45)	0.1 (0/20) 1 (0/20) 10 (0/20)[c] 100 (0/20)	↑ kidney wt ↑ kidney wt, ↓ bw none ↑ liver, kidney wt, ↓ bw	none none none liver, thyroid	none stated at any dose
1,2,4-Trichloro benzene CAS No. 120-82-1	SD rat, oral feed, 13 weeks, daily[g] (45)	0.1 (0/20) 1 (0/20) 10 (0/20)[c] 100 (0/20)	none none none ↑ kidney, liver wt	none none none liver, thyroid	none none none ↑ aniline hydroxylase, aminopyrene demethylase

SD= Sprague-Dawley; F344 = Fischer 344; GGT = gamma glutamyl transpeptidase; AP = alkaline phosphatase; GPT = glutamic-pyruvic transaminase; ALT = alanine aminotransferase; BUN = blood urea nitrogen; WBC = white blood cell; AST = aspartate aminotransferase; wt = weight, bw = body weight

[a] Category members are in bold face and surrogates are in regular type. References are in the species/exposure heading and are numbered in parentheses. Study details are found in the robust summaries (IUCLID Section 5.4). Data for surrogates are located in the robust summary set for 1,2,3-trichlorobenzene (CAS No. 87-71-6).

[b] In mg/kg/day; [c] No observable adverse effect level (NOAEL)

[d] Pituitary and thyroid changes subjectively graded as minimal to mild

[e] Pituitary and thyroid changes subjectively graded as minimal to moderate

[f] Pituitary and thyroid changes subjectively graded as mild to moderate

[g] Doses given are approximate

The characteristic liver effects are dose-dependent degeneration and necrosis of cetrilobular cells, lipid accumulation, and an increase in organ weight. Doses toxic to the liver also cause increased excretion of porphyrins in the urine and elevated liver enzymes in the serum. The characteristic kidney related changes include diffusely distributed, coagulative degeneration and necrosis of the proximal tubules, increased organ weight, and increased urine volume. Damage to hematopoetic tissue (bone marrow, thymus and spleen) and the thyroid are generally observed at higher doses. This includes atrophy of the lymphoid cells in the thymus and spleen, thymic necrosis, reduced leukocytes counts and elevated erythrocyte or platelet counts in blood. Damage to the GI mucosa is observed in the dog, but not other species. Subtle and subjectively graded changes in the pituitary have been noted in rats treated with 1,3-dichlorobenzene, but not the other chlorobenzenes.

Because adequate repeated dose oral toxicity studies have been performed on all category members, there is no need for additional testing.

4.5.2 Mutagenicity and Chromosomal Aberrations

All category members and surrogates have tested negative for mutagenicity in the Ames test (Table 8). Monochlorobenzene, and 1,2-, 1,3- and 1,4-dichlorobenzene also tested negative in a reverse mutation assay in E. coli. Therefore, no new in vitro mutagenicity testing is planned.

In vitro and/or in vivo tests to assess the ability of the category members and surrogates to cause chromosome damage also have been performed on all category members and/or surrogates (Table 8). All results of chromosomal aberration and/or sister chromatid exchange (SCE) assays in Chinese hamster ovary cells with monochlorobenzene, 1,2-dichlorobenzene, 1,4-dichlorobenzene, and 1,2,3- and 1,2,4-trichlorobenzene indicate that these materials are not cytogenetic toxicants (with the exception of an ambiguous result for 1,2-dichlorobenzene in the presence of metabolic activation). Results of in vivo cytogenicity tests with monochlorobenzene, and 1,3-dichlorobenzene were negative, and 1,2-dichlorobenzene were ambiguous.

Whereas the results of several well-conducted and reliable mouse micronucleus tests performed with monochlorobenzene, 1,2-dichlorobenzene, 1,4-dichlorobenzene or 1,2,4-trichlorobenzene were negative, a single study with a reliability rating of 4 gave a positive result for all category members and surrogates.

Taken together, the weight of evidence indicates that these materials are not mutagenic or genotoxic. Since at least one adequate in vitro or in vivo study has been performed to assess the cytogenicity of all category members, and the single positive result in the NMRI mouse mutagenicity test has been refuted by more reliable tests performed on four of the category members and surrogates, existing tests are considered sufficient to support a conclusion that the category members are not mutagenic or genotoxic. No new testing is planned.

4.5.3 Reproductive and Developmental Toxicity

Two generation reproductive toxicity studies (Table 9) have been performed with category members monochlorobenzene and 1,2- dichlorobenzene and the surrogates 1,4-dichlorobenzene and 1,2,4- trichlorobenzene. Reproductive organs from animals treated with 1,3-dichlorobenzene and 1,2,3- trichlorobenzene for 90 days also have been examined. Results of the reproductive studies with monochlorobenzene and 1,2,4- trichlorobenzene and the reproductive organ examinations from studies with 1,3-dichlorobenzene and 1,2,3- trichlorobenzene were unremarkable (Table 9). In a 2-generation reproductive toxicity study in rats, inhalation of

Table 8. Genotoxicity of category members and surrogates

Test/Organism	**Monochloro benzene CAS No. 108-90-7**	**1,2-Dichloro benzene CAS No. 95-50-1**	**1,3-Dichloro benzene CAS No. 541-73-1**	1,4-Dichloro benzene CAS No. 106-46-7	**1,2,3-Trichloro benzene CAS No. 87-61-6**	1,2,4-Trichloro benzene CAS No. 120-82-1
Ames (+/- S9)	Neg[a] (30,46,47)	Neg[b] (42, 46-50)	Neg[b] (46-49)	Neg[c] (49)	Neg[c] (49)	Neg[c] (49)
Reverse Mutation Assay E coli WP2(trp-, uVRA-) +/- S9	Neg (47)	Neg (47)	Neg (47)	Neg (47)	NP	NP
Chromosome Aberration (+/-S9) CHO Cell	Neg (51)	Neg (7)[d]	NP	Neg (52)	Neg (51)	Neg (51)
Sister chromatid exchange (+/-S9) CHO Cell	Pos (53)	Neg (-S9) (54) Ambig (+S9)[e] (54)	NP	Neg (52)	NP	NP
In vivo Cytogenicity B6C3F1 Mouse Chinese hamster Rat	 Ambig[f] (55) NP NP	 NP NP Neg (7)[d]	 NP Neg (10) NP	NP	NP	NP
Micronucleus (i.p.) B6C3F1 Mouse NMRI Mouse	 Neg (55,56) Pos[e] (57)	 Neg (55,56) Pos[e] (57)	 NP Pos[e] (57)	 NP Neg[g] (58) Pos[e] (57)	 NP Pos[e] (57)	 NP Neg[d,g] (59) Pos[e] (57)

Category members are in bold face and surrogates are in regular type. References are numbered in parentheses. Study details are found in the robust summaries (IUCLID Section 5.5). NP = not performed

[a] S. typhimurium TA98, TA100, TA1535, TA1537, TA1538

[b] S. typhimurium TA98, TA100, TA1535, TA1537, TA1538, UTH8414, 8413

[c] S. typhimurium TA98, TA100, TA1535, TA1537

[d] The study was not reviewed; [e]Study was given a reliability rating of 4

[f] Positive in one test and negative in another; [g] By oral administration

maternally toxic concentrations of 1,2-dichlorobenzene (150 and 400 ppm) was associated with decreased birth and/or lactational weight of F1 and F2 pups. In a similar study, inhalation of a maternally toxic concentration of 1,4-dichlorobenzene (538 ppm) was associated with decreased litter size, fetal weight, survival index, and numbers of liveborn pups. In the studies with 1,2- and 1,4-dichlorobenzene, there was no effect on reproductive parameters such as mating or fertility indices of males or females, the gestational index, the lactation index, or the number of copora lutea or implantation sites (including resorptions), suggesting that materials had no effect on fertility. Based on the structural and physical similarities between the members of the category and surrogates and organ toxicity data, it is expected that 1,3-dichlorobenzene and 1,2,3- trichlorobenzene also would not affect fertility, but may be fetotoxic at maternally toxic doses. No new reproductive toxicity testing is planned.

Results of the developmental toxicity studies (Table 10) on all category members and surrogates indicate that the chlorobenzenes are not embryotoxic or teratogenic at the doses tested. The only effects noted were minor skeletal variants in offspring of rats treated with maternally toxic doses

Table 9. Reproductive toxicity of category members and surrogates

Category Member[a]	Animal	Treatment	Effects
Monochloro benzene CAS No. 108-90-7 (60)	SD rat, 2 gen study	Inhal during mating, gestation and lactation 50, 150, 450 ppm	NOAEL (parental) = 50 ppm NOAEL (fetal) = 450 ppm 150 ppm (parental) - liver, kidney toxicity 450 ppm (parental) - liver, kidney, testicular toxicity. No effect on fertility
1,2-Dichloro benzene CAS No. 95-50-1 (61)	SD rat, 2 gen study	Inhal 6 h/d, 7 d/wk during mating, gestation and lactation 50, 150, 400 ppm	NOAEL (parental) < 50 ppm. NOAEL (fetal) =50 ppm (F1), 150 ppm (F2) 50 ppm (parental) - increased liver weight 150 ppm (parental) - liver, kidney toxicity 150 ppm (F1 pups) - decreased birth weight 400 ppm (parental)- liver, kidney toxicity, decreased bw. No effect on reproductive parameters. 400 ppm (pups) - decreased birth and lactational weight
1,3-Dichloro benzene CAS No. 541-73-1 (43)	SD rat, examination of reproductive organs	Gavaged daily for 90 days 9, 37, 147, 588 mg/kg	NOAEL (reproductive organs) = 147 mg/kg bw 588 mg/kg - increased testicular weights. No histological lesions.
1,4-Dichloro benzene CAS No. 106-46-7 (62)	SD rat, 2 gen study	Inhal 6 h/d, 7 d/wk during mating, gestation and lactation 66.3, 211, 538 ppm	NOAEL (parental) < 66.3 ppm. NOAEL (fetal) = 211 ppm 66.3 ppm (parental) - kidney toxicity, increased liver wt 211 (parental) - liver, kidney toxicity, reduced bw 538 ppm (parental)- reduced body weights, food consumption, liver, kidney toxicity 538 ppm (pups) - decreased number live born pups/litter, decreased litter size, body weight, increased stillborn and postnatal deaths.
1,2,3-Trichloro benzene CAS No. 87-61-6 (45)	SD rat, examination of reproductive organs	Oral diet, approx. 0.1, 1, 10 and 100 mg/kg/day for 91 days	NOAEL (reproductive organs) = 100 mg/kg bw 100 mg/kg (systemic) - increased liver, kidney wt, decreased bw. Lesions in liver and thyroid.
1,2,4-Trichloro benzene CAS No. 120-82-1 (63)	Charles River rat, 2 gen study	Drinking water from birth of F0 generation to weaning of F2 25, 100, 400 ppm	NOAEL (parental) = 100 ppm NOAEL (fetal) = 400 ppm 400 ppm (parental) - increased adrenal wt. No effect on fertility

[a] Category members are in bold face and surrogates are in regular type. References are numbered in parentheses. Study details are found in the robust summaries (IUCLID Section 5.8).
NOAEL = No observable adverse effect level; SD = Sprague Dawley

of monochlorobenzene (590 ppm) and 1,2-dichlorobenzene (400 ppm) and an increased incidence of retroesophageal right subclavian artery (a minor variant in the circulatory system) in offspring of rabbits treated with a maternally toxic dose of 1,4-dichlorobenzene (800 ppm). The authors of each of these studies concluded that these effects were not indicative of a teratogenic response. However, the results suggest that mild fetotoxicity may occur at maternally toxic doses of the category members. No additional developmental testing is planned.

Table 10. Developmental Toxicity of category members and surrogates

Category Member[a]	Animal	Treatment	Effects[b]
Monochloro benzene CAS No. 108-90-7	NZW Rabbit (64)	10, 30, 75, 210, 590 ppm inhal., 6 hr/d, d 6-18 of gest.	NOAEL (maternal) = 75 ppm. Increased liver wt at higher concentrations. NOAEL (teratogenicity, fetotoxicity) = 590 ppm.
	F344 rat (64)	75, 210, 590 ppm inhal., 6 hr/d, d 6-15 of gest.	NOAEL (maternal) = 210 ppm. Weight loss and increased liver weight at higher concentrations. NOAEL (fetotoxicity) = 210 ppm. Increased incidence of some skeletal variations at 590 ppm. NOAEL (teratogenicity) = 590 ppm
1,2-Dichloro benzene CAS No. 95-50-1	NZW Rabbit (65)	100, 200, 400 ppm inhal., 6 hr/d, d 6-18 of gest.	NOAEL (maternal) < 100 ppm. Decreased BW gains at all doses. NOAEL (teratogenicity, fetotoxcity) = 400 ppm
	F344 rat (65)	100, 200, 400 ppm inhal., 6 hr/d, d 6-15 of gest.	NOAEL (maternal) < 100 ppm. Increased liver wt at 100 and 400 ppm and decreased BW at all doses. NOAEL (fetotoxicity) = 200 ppm. Increased incidence of delayed ossification of cervical ribs at 400 ppm NOAEL (teratogenicity) = 400 ppm
	SD rat (66)	50, 100, 200 mg/kg, gavage, d 6-15 of gest.	NOAEL (teratogenicity) = 200 mg/kg[c]
1,3-Dichloro benzene CAS No. 541-73-1	SD rat (66)	50, 100, 200 mg/kg, gavage, d 6-15 of gest.	NOAEL (teratogenicity) = 200 mg/kg[c]
1,4-Dichloro benzene CAS No. 106-46-7	NZW Rabbit (65)	100, 300, 800 ppm by inhal., 6 hr/d, d 6-18 of gest.	NOAEL (maternal) = 300 ppm. Decreased maternal weight gain at 800 ppm. NOAEL (fetotoxicity) = 300 ppm. Increased incidence of retroesophageal right subclavian artery (a variation) at 800 ppm NOAEL (teratogenicity) = 800 ppm
	SD rat (66)	50, 100, 200 mg/kg, gavage, d 6-15 of gest.	NOAEL (teratogenicity) = 200 mg/kg[c]
1,2,3-Trichloro benzene CAS No. 87-61-6	SD rat (67)	150, 300 and 600 mg/kg, gavage, d 6-15 of gest.	NOAEL (maternal) = 150 mg/kg. Decreased hemoglobin, thyroid toxicity, and increased liver wt at higher concentrations. NOAEL (teratogenicity, fetotoxicity) = 600 mg/kg
1,2,4-Trichloro benzene CAS No. 120-82-1	SD rat (67)	75, 150 and 300 mg/kg, gavage, d 6-15 of gest.	NOAEL (maternal) = 75 mg/kg. Decreased hemoglobin, thyroid toxicity, and increased liver wt at higher concentrations. NOAEL (teratogenicity, fetotoxicity) = 300 mg/kg

F344 = Fischer 344; NZW = New Zealand White; SD= Sprague-Dawley.
[a] Category members are in bold face and surrogates are in regular type. References are indicated numerically in parentheses. Study details are found in the robust summaries (IUCLID Section 5.9; data for 1,4 dichlorobenzene are in the file for 1,3-dichlorobenzene).
[b] NOAELs for fetotoxicity were assigned by the reviewer (unless listed as assigned by study personnel in summaries)
[c] Assigned a reliability rating of 4 (and therefore is not sufficient). There were not enough data to assign a NOAEL for fetotoxicity. Data came from an abstract.

4.5.4 Additional Data

4.5.4.1 Carcinogenicity

Monochlorobenzene and 1,2-dichlorobenzene were administered to rats and mice (60 and 120 mg/kg/day) for 103 weeks in separate NTP studies. 1,2-dichlorobenzene was negative for carcinogenicity in both rats and mice (NTP, 1985b), and monochlorobenzene was not tumorigenic in male and female mice and female rats (Kluwe et al., 1985, NTP, 1985a). Male rats given 120 mg/kg/day monochlorobenzene had an increased incidence of benign neoplastic liver nodules at 120 mg/kg/day, which was deemed an equivocal response by the NTP. Meta (1,3-) dichlorobenzene and 1,2,3-trichlorobenzene have not been tested in long-term carcinogenicity studies.

4.5.5 Test Plan for Mammalian Toxicity

For this category, adequate tests have been performed for most of the endpoints (Table 1). Based on the structural similarities of the molecules and similar eco- and mammalian toxicity profiles of the category members and surrogates, tests already performed on category members and surrogates are predictive of effects for the chlorobenzenes lacking experimental data. No new testing is recommended due to the well-characterized effects of these chlorobenzenes.

5. Conclusion

The four chemical substances that comprise the Chlorobenzenes Category all have a common molecular structure. The only difference in the molecules is in the number of chlorine atoms on the aromatic ring and their relative (isomeric) positions. The same is true for the two surrogates. All four category members have similar chemical/physical properties, estimated and experimental values for environmental fate parameters, and toxicological profiles.

In summary, the data provided in the robust summaries and test plan follows a pattern that is consistent with the close molecular similarity of the category members and surrogates. The data confirm the validity of the category. The robust summary set readily facilitates extrapolation of available data and supports the modeling that was used to fill the few experimental data gaps; therefore no new testing is required.

6. References

1. Klimisch HJ, Andreae M and Tillmann U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Reg Tox Pharm 25:1-5.

2. Solutia Material Safety Data Sheet

3. IUCLID data set from the European Chemicals Bureau, creation date 10-FEB-2000.

4. BUA. 1993. CDCh-Advisory Committee on Existing Chemicals of Environmental Relevance Report 54 (November 1990). S. Hirzel Wissenschaftliche Verlagsgesellschaft, Stuttgart, Germany. pp. 4, 5, 99, 100, 107.

5. Leo A, Hansch C, Elkins D. 1971. Partition coefficients and their uses. Chem Rev. 71, 525, 526, 555, 528, 614.

6. Hansch C, Leo A. 1979. Substituent constants for correlation analysis in chemistry and biology. John Wiley and Sons, New York.

7. IUCLID data set from NICNAS, creation date 23-AUG-2001

8. BUA. 1993. CDCh-Advisory Committee on Existing Chemicals of Environmental Relevance (BUA) Report 53 (September, 1990). S. Herzel Wissenschaftliche Verlagsgesellschaft, Stuttgart, Germany, pp. 6, 7, 111, 118-119, 126.

9. McCrady JK, McFarlane C, Lindstrom FT. 1987. The transport and affinity of substituted benzenes in soybean stems. J Exp Bot 38:1875-1890.

10. IUCLID data set from the European Chemicals Bureau, creation date 11-FEB-2000.

11. Carpenter M. 1988. Determination of octanol water partition coefficient of ^{14}C-p-dichlorobenzene. ABC Laboratories, Inc. Report No. 37401, dated Nov. 9, 1988.

12. Material Safety Data Sheet from Compendium of safety data sheets from VCH Publishers, Inc,. Deerfield Beach, FL.

13. MacLeod M and Mackay D.1999. An Assessment of the Environmental Fate and Exposure of Benzene and Chlorobenzenes in Canada. Chemosphere 38:1777-1796.

14. Warner HP, Cohen JM, Ireland JC. 1987. Determination of Henry's law constants of selected priority pollutants. EPA Report Nr. 600/D-87/229 S. 1-14.

15. Ashworth RA, Howe GB, Mullins ME, Rogers TN. 1988. Air-water partitioning coefficients of organics in dilute aqueous solutions. J Hazard Mater 18:25-36.

16. Macleod M. and Mackay D.1999. An Assessment of the Environmental Fate and Exposure of Benzene and the Chlorobenzenes in Canada, Chemosphere 38:1777-1796.

17. Fieser LF and Fieser M. 1960. Organic Chemistry. DC Heath and Company, p 625.

18. Fackler PH. 1989. Springborn Life Sciences Report No. 89-4-2965. Study No. 10823-0189-6109-715, dated 26 April 1989.

19. Calamari D, Galassi S, Setti F, Vighi M. 1983. Toxicity of selected chlorobenzenes to aquatic organisms. Chemosphere 12:253-262

20. Jones W. 1990. Investigation of the lethal effects of the test material chlorobenzene to the rainbow trout (static test) according to OECD Guideline 203. NATEC Project NA 899434, dated April 1990.
21. Galassi S, Vighi M. 1981. Testing toxicity of volatile substances with algae. Chemosphere 10:1123-1126.
22. Geiger DL, Poirier SH, Brooke LT, Call DJ. 1986. Acute toxicities of organic chemicals to fathead minnows (Pimephales promelas). Volume III. Center for Lake Superior Environmental Studies, University of Wisconsin-Superior.)
23. Richter JE, Peterson SF, Kleiner CF. 1983. Acute and chronic toxicity of some chlorinated benzenes, chlorinated ethanes, and tetrachloroethylene to Daphnia magna. Arch Environ. Contam. Toxicol. 12: 679-684.
24. Suprenant DC. 1988. Acute toxicity of 1,2,3- trichlorobenzene to fathead minnow (Pimephales promelas) under flow-through conditions. Springborn Life Sciences Inc. Report 88-6-2732, dated July 12, 1988.
25. Bobra AM, Shiu WY, Mackay D. 1983. A predictive correlation for the acute toxicity of hydrocarbons and chlorinated hydrocarbons to the water flea. Chemosphere 12:1121-1129.
26. Suprenant DC. 1988. Acute toxicity of 1,2,3- trichlorobenzene to mysid shrimp (Mysidopsis bahia) under flow-through conditions. Springborn Life Sciences Inc. Report 88-4-2705, dated June 28, 1988.
27. Suprenant DC. Acute toxicity of 1,2,4 - trichlorobenzene to mysid shrimp (Mysidopsis bahia) under flow-through conditions Springborn Life Sciences, Inc. Report 88-4-2704, dated June 28, 1988
28. Birch MD. Younger Laboratories report on acute oral, dermal and inhalation toxicity and skin and eye irritation for monochlorobenzene (technical). Project No. Y-76-14, dated May 26, 1976.
29. Kluwe WM, Dill G, Persing R, Peters A. 1985. Toxic responses to acute, subchronic, and chronic oral administrations of monochlorobenzene to rodents. J Toxicol Environ Health 15:745-767
30. NTP. 1985. NTP Technical Report on the toxicology and carcinogenesis studies of chlorobenzene (CAS No. 108-90-7) in F344/N rats and B6C3F1 mice (gavage studies). NIH Publication No. 86-2517.
31. Bonnet P, Raoult G, Gradiski D. 1979. Concentrations lethales 50 des principaux hyddrocarbures aromatiques. Arch des maladies professionnelles de medecine du travail. 40(8,9):805-810 [French].

32. Bonnet P, Morele Y, Raoult G, Zissu D, Gradiski D. 1982. Determination de la concentration lethale50 des principaux hydrocarbures aromatiques chez le rat. Arch mal prof. 43(4):261-265 [French].
33. Hollingsworth RL, Rowe VK, Oyen F, Torkelson TR, Adams EM. 1958. Toxicity of o-dichlorobenzene. Arch Ind Health 17:180-7.

34. Birch MD. 1980. Nonclinical Laboratory Study Final Report. Test material: m-dichlorobenzene. Younger Laboratories Incorporated Project Number Y-79-90. Dated November15, 1980.

35. Gaines TB and Linder RE. 1986. Acute toxicity of pesticides in adult and weanling rats. Fund Appl Toxicol 7:299-308.

36. Newton PE. 1990. An acute inhalation toxicity study of para-dichlorobenzene in the rat. Biodynamics Inc. Project No. 89-8230, dated March 2, 1990.

37. Brown VKH, Muir C, Thorpe E. 1969. The acute toxicity and skin irritant properties of 1,2,4-trichlorobenzene. Ann Occup Hyg 12:209-212.

38. Roloff MV. 1980. Subchronic inhalation toxicity study of monochlorobenzene to male and female dogs. Monsanto Environmental Health Laboratory Project No 790015/DMEHML-79-025, dated Oct 30, 1980.

39. Hayes WC, Hanley TR Jr, Gushow TS, Johnson KA, John JA. 1985. Teratogenic potential of inhaled dichlorobenzenes in rats and rabbits. Fund Appl Toxicol 5: 190-202.

40. Knapp WA. 1967. 13-week oral administration – dogs monochlorobenzene final report. Hazleton Laboratories, Inc. Project No. 241-105. Feb 24, 1967.

41. Robinson M, Bercz JP, Ringhand HP. 1991. Ten- and ninety-day toxicity studies of 1,2-dichlorobenzene administered by oral gavage to Sprague-Dawley rats. Drug Chem Toxicol. 14:83-112.

42. NTP.1985. Toxicology and carcinogenesis studies of 1,2-dichlorobenzene (CAS No. 95-50-1) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, N.C. National Toxicology Program. NTP TR-255. NIH Publication No. 86-2511.

43. McCauley PT, Robinson M, Daniel FB, Olson GR. 1995. Toxicity studies of 1,3-dichlorobenzene in Sprague-Dawley rats. Drug Chem Toxicol 18(2-3): 201- 221.

44. NTP. 1985. Toxicology and carcinogenesis studies of 1,4-dichlorobenzene (CAS No. 106-46-7) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, N.C. National Toxicology Program. NTP TR-319. NIH Publication No. 87-2575.

45. Cote M, Chu I, Villeneuve DC, Secours VE, Valli VE. 1988. Trichlorobenzenes: Results of a thirteen week feeding study in the rat. Drug Chemical Toxicol 11:11-28.

46. Shimizu M, Yasui Y, Matsumoto N. 1983. Structural specificity of aromatic compounds with special reference to mutagenic activity in Salmonella typhimurium - a series of chloro- or fluoro-nitrobenzene derivatives. Mut. Res. 116:217-238.

47. Simmon VF, Riccio ES, Peirce MV. 1979. In vitro microbiological genotoxicity assays of chlorobenzene, m-dichlorobenzene, o-dichlorobenzene, and p-dichlorobenzene. SRI International Project LSU-7558, dated May 1979.

48. Connor TH, Theiss JC, Hanna HA, Monteith DK, Matney TS. 1985. Genotoxicity of organic chemicals frequently found in the air of mobile homes. Toxicol Lett. 25:33-40.

49. Haworth S, Lawlor T, Mortelmans K, Speck W, Zeiger E. 1983. Salmonella mutagenicity test results for 250 chemicals. Environ Molec Mutagen Suppl 1:3-142.

50. Flowers LJ. 1978. Final report on Salmonella mutagenicity assay of o-dichlorobenzene (technical). Monsanto Project No. LF-78-146, Dated Aug 14, 1978.

51. Sofuni T, Hayashi M, Matsuoka A, Sawada M, Hatanaka M, Ishidate M Jr. 1985. Mutagenicity tests on organic chemical contaminants in city water and related compounds. II. Chromosome aberration tests in cultured mammalian cells. Bull National Inst Hyg Sci (Tokyo) 103:64-75.

52. Galloway SM, Armstrong MJ, Reuben et al. 1987. Chromosome aberrations and sister chromatid exchanges in Chinese Hamster Ovary Cells: Evaluations of 108 Chemicals. Environ Mol Mutagen 10:1-175.

53. Loveday K.S. et al. 1989. Environ. Mol. Mutagen. 13:60-94.

54. Loveday KS, Anderson BE, Resnick MA, Zeiger E. 1990. Chromosome aberration and sister chromatid exchange tests in chinese hamster ovary cells in vitro. V. Results with 46 chemicals. Environ Mol Mutagen 16: 272-303.

55. Shelby MD and Witt KL. 1995. Comparison of results from mouse bone marrow chromosome aberration and micronucleus tests. Environ Molec Mutagen 25:302-313.

56. Shelby MD, Erexson GL, Hook GJ, Tice RR. 1993. Evaluation of a three-exposure mouse bone marrow micronucleus protocol: results with 49 chemicals. Environ Molec Mutagen 21:160-179.

57. Mohtashamipur E, Triebel R, Straeter H, Norpoth K. 1987. The bone marrow clastogenicity of eight halogenated benzenes in male NMRI mice. Mutagen 2:111-113.

58. Tegethoff K, Herbold BA, Bomhard EM. 2000. Investigations on the mutagenicity of 1,3-dichlorobenzene and its main metabolite 2,5-dichlrophenol in vivo and in vitro. Mut Res. 470:161-167

59. CCR. 1990. Report No R. 4965, Project No. 165600.

60. Nair RS, Barter JA, Schroeder RE, Knezevich A, Stack CR. 1987. A two-generation reproduction study with monochlorobenzene vapor in rats. Fund Appl Toxicol 9:678-686.

61. Schroeder RE, Daly IW. 1989. An inhalation two-generation reproduction study in rats with orthodichlorobenzene. Bio/dynamics Inc. Project No. 87-3157, dated Jan 13, 1989.

62. Tyl RW, Neeper-Bradley TL. 1989. Two-generation reproduction study of inhaled paradichlorobenzene in Sprague-Dawley (CD) rats. Bushy Run Research Center Project Report 51-593, dated January 16, 1989

63. Robinson KS, Kavlock RJ, Chernoff N, Gray E. 1981. Multigeneration study of 1,2,4-trichlorobenzene in rats. J Toxicol Environ Health 8:489-500.)

64. John JA, Hayes WC, Hanley TR Jr, Johnson KA, Gushow TS, Rao KS. 1984. Inhalation teratology study on monochlorobenzene in rats and rabbits. Toxicol Appl Pharmacol 76:365-373.

65. Hayes WC, Hanley TR Jr, Gushow TS, Johnson KA, John JA. 1985. Teratogenic potential of inhaled dichlorobenzenes in rats and rabbits. Fund Appl Toxicol 5: 190-202.

66. Ruddick JA, Black WD, Villeneuve DC, Valli VE. 1983. A teratological evaluation following oral administration of trichloro- and dichlorobenzene isomers to the rat. Teratology 27 (2): 73 A (abstract).

67. Black WD, Valli VEO, Ruddick JA, Villeneuve DC. 1988. Assessment of teratogenic potential of 1,2,3- and 1,2,4- and 1,3,5- trichlorobenzenes in rats. Bull Environ Contam Toxicol 41:719-726